Dissertation on

A STUDY OF AUTONOMIC DYSFUNCTION AND QT PROLONGATION IN HIV INFECTION

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CERTIFICATE

This is to certify that the dissertation titled **"AUTONOMIC DYSFUNCTION AND QT PROLONGATION IN HIV INFECTION"** is the bona fide original work of **Dr. P. VINODH KUMAR** in partial fulfillment of the regulation for M.D. Branch–I (General Medicine) Examination of the Tamilnadu Dr. M.G.R Medical University to be held in MARCH 2007. The Period of study was from august 2005 to may 2006.

Prof. D. RAJASEKARAN, M.D
Professor Of Medicine,
Madras Medical College and Research Institute,
Govt. General Hospital,
Chennai – 600 003.

Prof. P. THIRUMALAI KOLUNDHU SUBRAMANIAN, M.D
Director,
Institute of Internal Medicine,
Madras Medical College and Research Institute,
Govt. General Hospital,
Chennai -600 003.

Prof. KALAVATHY PONNIRAIVAN, B.Sc, M.D
Dean
Institute of Internal Medicine,
Madras Medical College and Research Institute,
Govt. General Hospital,
Chennai -600 003.

DECLARATION

I, **Dr. P. VINODH KUMAR,** solemnly declare that dissertation titled **"AUTONOMIC DYSFUNCTION AND QT PROLONGATION IN HIV INFECTION"** is a bonafide work done by me at Madras Medical College and Govt. General Hospital from August 2005 to May 2006 under the guidance and supervision of my unit chief **Prof. D. RAJASEKARAN, M.D.,** Professor of Medicine.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of regulation for the award of M.D. Degree (Branch – I) in General Medicine.

Place : Chennai.

Date :

Dr. P. VINODH KUMAR

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CONTENT

ABBREVIATION

AIDS Syndrome	-	Acquired Immuno Deficiency
AN	-	Autonomic Neuropathy
BMI	-	Body Mass Index
BP	-	Blood Pressure
CYP	-	Cytochrome P
DM	-	Diabetes Mellitus
ELISA	-	Enzyme Linked Immunosorbent Assay
GI	-	Gastro Intestinal
HAART	-	Highly Active Antiretroviral Therapy
HIV	-	Human Immuno Deficiency Virus
HR	-	Heart Rate
LQTS	-	Long QT Syndrome
NACO	-	National AIDS Control Organization
OH	-	Orthostatic Hypotension
PN	-	Peripheral Neuropathy
QSART	-	Quantitative Sudomotor Axon Reflex Test
SHT	-	Systemic Hypertension
TDP	-	Torsades de pointes
VCTC	-	Voluntary counseling and testing centre

Introduction

INTRODUCTION

HIV has indeed turned into on global pandemic. In India alone the problem is waiting to explode what with an estimated population of about 5,700,000 infected with HIV[1]. An estimated 6 million cases will be infected with HIV by year 2010[2]. This issue is important since we are seeing patients infected with the disease almost on a daily basis and these patients are subjected to various invasive procedures.

It has been well documented that HIV infection is associated with Autonomic Dysfunction[3,4].

Cardiovascular Autonomic dysfunction has been demonstrated to severely debilitated HIV infection patients[3,4,6] and may also be associated with life threatening cardio respiratory arrest following invasive diagnostic procedure[5].

Despite the possible significance of this findings and the suggestion by others of autonomic dysfunction in HIV infection, little research has been undertaken on this topic, specifically in the Indian subcontinent.

A higher prevalence of QT prolongation has been reported in HIV/ AIDS patients and also the cause of the sudden death

in HIV is ascribed to QT prolongation with risk for ventricular arrhythmias[7,8]. Most of the QT prolongation in HIV is related to drug used in treatment. Whether QT prolongation occurs primarily in HIV infection or as a manifestation of Autonomic dysfunction is not studied extensively except a few studies[9].. We investigated the presence of cardiovascular autonomic dysfunction and its relation to QT prolongation in patients attending our clinics and admitted in wards at various stages of HIV infection.

Aim and Objectives

AIMS AND OBJECTIVES

1. To evaluate the presence and the extent of autonomic dysfunction in our hospital based population infected with HIV, compared with age and sex matched seronegative controls.
2. To correlate the degree of dysfunction with the stage of HIV infection.
3. To evaluate the presence of QT interval prolongation in HIV/AIDS patients.
4. To investigative the relationship between autonomic dysfunction and QT prolongation.

Review of Literature

REVIEW OF LITERATURE

In spite of the insight of the 19th century physiologist, Gaskell (1886), Bayliss and Starling (1899)[67] into the autonomic nervous system it was not until 1925 that a real understanding of the clinical presentation of autonomic failure emerged. This work came from careful clinical investigations carried out by Bradbury and Eggleton. From our current vantage point it is remarkable how thoroughly these investigators were able to define their patient's illness using a battery of bedside tests and laboratory investigations. Their contribution remains the single most intellectual achievement in our understanding of clinical autonomic failure.

However major advances have been made since the early 1960's that make it necessary to revive our thinking about the mechanism of autonomic transmission and that have significant implications for our understanding of our disease involving the autonomic nervous disease and treatment. These advances include

1. The discovery of non adrenergic, non cholinergic nerves and the later recognition of a multiplicity of neuro transmitters. E.g. Monoamines, purines and nitric oxide

(Burnstock et al 1964[68],Burnstock and Milner 1992 ; Rand, 1992; Snidder, 1992)

2. The concept of neuromodulation where locally released agents can alter neuro transmission either by modulation of the amount of transmitters released (Kaczmarek and Leviton 1987)[69].
3. Recognition of the importance of the sensory motor nerve regulation of activity in many organs including lung, heart, ganglion and many blood vessels (Maggi and Meli 1988[70], Burnstock 1990)
4. Recognition of the intrinsic ganglion (e.g. Heart and airways) containing integrated circuits capable of sustaining and modulating sophisticated local activities (Burnstock et al, 1987)[71].

In addition to these concepts, the discovery by Furchgott that substances released from endothelial cells play an important role in addition to autonomic nerves in control of local blood flow (Furchgott and Zawadski 1983, Ralevic and Burnstock 1993) and the later identification of nitric oxide as the major endothelium derived relaxing factor (Palmer et al 1988) shift the earlier emphasis on central control mechanisms, towards greater considerations of the sophisticated local peripheral control mechanisms.

HIV infection may be associated with abnormalities of Autonomic nervous system, particularly in advanced disease. The prevalence of Autonomic dysfunction in HIV varies from 5 to 77% according to the definition[10]. These abnormalities were first brought to our attention by Craddock et al.[5] who described syncopal reactions in AIDS patients who underwent fine needle aspiration of lung. These syncopal reactions were similar to typical vasovagal reactions and cardiorespiratory arrests following invasive procedures such as general and epidural anaesthesia. At the same period, various reports by of Dysautonomia in HIV was also published [3,4].

These studies have been done mostly on white population, with a very few studies on non white population[57,58] , despite the fact that there appears to be a significant difference in the autonomic function between two ethnic groups[64].

HIV AND PERIPHERAL NERVOUS SYSTEM

Neuromuscular disorder are the most frequent of the neurological complications that occur in association with HIV infection and AIDS[18,65]. Inflammatory Demyelinating polyneuropathy (IDP) may be the initial clinical manifestation occuring at the time of HIV seroconversion.

The frequency of distal symmetrical polyneuropathy (DSP) increases with decline in CD4 lymphocyte count and progression to AIDS[66]. In severely immunosuppressed patients (CD4 lymphocyte count <50 cells/mL), cytomegalovirus (CMV) may directly infect peripheral nerves, presenting as progressive polyradiculopathy (PP) or mononeuropathy multiplex (MM).

Peripheral neurophaties are common and may complicate HIV infection at each of its stages. Even during earliest state, at or near the time of seroconvertion, a variety of neuropathies have been described, although their incidence is low**.** These include brachial – plexopathy, mononeuritis multiplex involving peripheral or cravial neves and polynueropathy[13,14,15].

1) Distal Symmetrical Polyneuropathy

Distal symmetrical polyneuropathy (DSP) may be clinically diagnosed in approximately 25%-30% of patients with AIDS. The incidence and prevalence of DSP increases with the progressive immuno suppression that characterizes HIV-infection. The pathogenesis of AIDS-associated DSP is unknown. Numerous factors, including advanced age,

nutritional status, chronic disease, low hemoglobin level, HIV itself, neurotoxic cytokines, HIV glycoprotein gp-120, and low CD4 counts, have been correlated with clinical and electrophysiological presence of peripheral nervous system (PNS) dysfunction . The dose-dependent neurotoxicity of these agents may be the result of interference with mitochondrial DNA synthesis, possibly associated with reduced levels of acetyl-carnitine . Patients with a previous history of neuropathy are more susceptible to the peripheral nerve toxicity of these agents.

2) Inflammatory Demyelinating Polyneuropathy

Inflammatory demyelinating polyneuropathy (IDP) is an infrequent complication of HIV infection. It is clinically characterized by: (a) rapidly progressive muscle weakness involving two or more extremities, (b) generalized areflexia, (c) cranial nerve involvement (e.g. bilateral facial nerve paresis) . The acute form (AIDP) often occurs at the time of HIV seroconversion. The chronic form (CIDP) has a slower onset and gradual progression.

3) Progressive Polyradiculopathy

Progressive polyradiculopathy (PP) occurs mainly in late stages of AIDS disease. Patients with PP generally present with radiating pain and paresthesias in the cauda equina distribution, rapidly progressive flaccid paraparesis, lower extremity areflexia, mild sensory loss, and sphincter dysfunction, often manifesting as urinary retention. In certain occasions a thoracic sensory level is present, suggesting concurrent myelopathy.

4) Mononeuropathy Multiplex (MM)

Patients with MM present with the acute onset of multifocal sensory or motor abnormalities in the distribution of cranial, mixed or cutaneous nerves. The form of mononeuropathy multiplex (MM) that occurs in relatively immunocompetent patients (CD4 lymphocyte counts greater than 200 cells/ml) is probably mediated by immune mechanisms.

5) Diffuse Infiltrative Lymphocytosis Syndrome

Diffuse infiltrative lymphocytosis syndrome (DILS) is an unusual complication of HIV infection. It is characterized by CD8 hyperlymphocytosis that may involve peripheral nerve. DILS neuropathy may present as: symmetric or asymmetric

sensorimotor neuropathy, distal sensory neuropathy, mononeuritis multiplex or demyelinating polyneuropathy.

6) Autonomic Neuropathy

Several studies indicate that autonomic dysfunction, while often subclinical, is common in HIV infection, particularly in late stages of disease[36]. Autonomic neuropathy has been reported in AIDS patients often in conjunction with more general sensory polyneuropathy [12,26]. Parasympathetic autonomic nervous system manifestations include resting tachycardia, impotence, and urinary dysfunction. Sympathetic autonomic nervous system dysfunction is characterized by orthostatic hypotension, syncope, diarrhea, and anhidrosis.

Pathogenesis

Multiple factors may be involved in the mechanism of autonomic dysfunction, including central and peripheral nervous system pathology, dehydration, malnutrition and drugs (e.g. vincristine, tricyclic antidepressants, and pentamidine).

Apparently much more common is the development of demyclinating neuropathies during the asymptomatic or latent phase of HIV infection[16,17]. During the late stages the most common neuropathy is distal, predominantly sensory axonal

neuropathy [16,18, 19]. This is usually a late complication and occurs in the setting of AIDS. Characteristically sensory symptoms far exceed either sensory or motor dysfunction. The pathogenesis of this disorder is uncertain, but is related to cytotine dysregualtion, either alone or in concert with HIV-infection of nerve or dorsal root ganglia [19,20].

Several Antiretroviral drugs including didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) ddI, 7have peripheral neuropathy as a major, dose-related side effect[21,22,23]. During late stages more serious infections neuropathies related to CMV are known to occur [12,24,25].

Prevalence of cardiac autonomic neuropathy and sensori motorneuropathy is about 15% each in HIV infection. The changes in CD4 count and respiratory arrhythmia also correlated significantly[36].

Autonomic nervous system

The autonomic nervous system conveys sensory impulses from the blood vessels, the heart and all of the organs in the chest, abdomen and pelvis through nerves to other parts of the brain (mainly the medulla, pons and hypothalamus). These impulses often do not reach our consciousness, but elicit

largely automatic or reflex responses through the efferent autonomic nerves, thereby eliciting appropriate reactions of the heart, the vascular system, and all the organs of the body to variations in environmental temperature, posture, food intake, stressful experiences and other changes to which all individuals are exposed. There are two major components of the autonomic nervous system, the sympathetic and the parasympathetic systems. The afferent nerves subserving both systems convey impulses from sensory organs, muscles, the circulatory system and all the organs of the body to the controlling centers in the medulla, pons and hypothalamus

The impulses of the parasympathetic system reach the organs of the body through the cranial nerves # 3, 7, 9, & 10, and some sacral nerves to the eyes, the gastrointestinal system, and other organs. The sympathetic nerves reach their end-organs through more devious pathways down the spinal cord to clusters of sympathetic nerve bodies (ganglia) alongside the spine where the messages are relayed to other nerve bodies (or neurons) that travel to a large extent with the blood vessels to all parts of the body. Through these nervous pathways, the autonomic nerves convey stimuli resulting in largely unconscious, reflex, bodily

adjustments such as in the size of the pupil, the digestive functions of the stomach and intestines, the rate and depth of respiration and dilatation or constriction of the blood vessels. The function of Autonomic nervous system in its regulation of the internal organs is to a high degree independent. When the autonomic nervous are interrupted, these organ continue to function, but they are no longer as effective in maintaining homeostasis and adapting to the demands of changing internal condition and external stress.

Autonomic dysfunction

Impairment of Autonomic function may occur as part of the more common acute or chronic peripheral neuropathies (eg; Diabetic, alcoholic-nutritional, amyloid, Gullain-Barre syndrome, infections, heavy metal toxic and porrphyrias. Diseases of the peripheral nervous system may affect the circulation in two ways: the nerves from baroreceptors may be affected, interrupting normal homeostatic reflexes on the afferent side or post ganglionic efferent sympathetic fibres may be involved in the spinal nerves. The severity of the autonomic failure need not parallel the degree of motor weakness.

Autonomic dysfunction that accompanies diabetic neuropathy is the one that has extensively evaluated [27,28,29].

Duchen and Coworkers[30] attributed the autonomic disorder to vacuolization of sympathetic ganglionic nervous, cell nervous and inflammation, loss of myelinated fibres in the vagi and white rami communicates, and loss of lateral horn cells in the spinal cord. They believe the later changes to be secondary.

Clinical features of Autonomic Dysfunction can be divided as follows[38]

(i) **Cardiovascular symptoms:** Postural hypotension, vertigo, syncope.

(ii) **Upper GI symptoms**: Dysphagia, nausea, emesis, early satiety, bloating.

(iii) **Lower GI symptoms**: Diarrhea, constipation involuntary loss of stools and incomplete evacuation.

(iv) **Urological symptoms**: Dysuria, involuntary dribbling of urine, prolonged dribbling incomplete bladder emptying, impotence.

(v) **Others**: Hypohydrosis, hyperhydrosis, Gustatory sweating.

Physiological basis for testing Abnormalities of Autonomic Nervous System

(i) Responses of Blood pressure and Heart Rate to changes imposture and breathing.

McLeod and Tuck[31] state that in changing from recumbent to standing position a fall of more than 30mmHg systolic and 15 mmHg diastolic is abnormal; others give figures

of 20 and 10mmHg. This excessive drop in Blood pressure indicates inadequate sympathetic vasoconstrictor activity. In response to the induced drop in blood pressure, the pulse rate normally increases: The failure of rise in heart rate in response to drop in blood pressure withstanding is a good indication of vagal nerve dysfunction[34]. In addition the pulse after rising initially in response to upright posture slows after about 15 beats to reach a stable rate by the 30th beat. The ratio of R-R interval in the ECG, corresponding to the 30th and the 15th beats is an even more sensitive measure of the integrity of Vagal inhibition the sinus node. A ratio in nonelderly of less than 1.05 is usually abnormal, indicating loss of vagal tone[34].

Another simple procedure for quantization of vagal function consists of measuring the variation in heart rate during deep breathing. Normally heart rate varies by as many as 15 beats per minute or even more, between expiration and inspiration; differences of less than 10 beats per minute may be abnormal. A yet more accurate test of vagal function is measurement of ratio of the longest R-R interval during forceful flow expiration to the shortest R-R interval during inspiration and deviation of expiration inspiration (E:I ratio) up to Age 40 E:I of less than 1:2 as abnormal[34].

In Valsalva maneuvers, the subject exhales into a manometer or against a closed glottis for 10-15 seconds. Creating a markedly positive intra thoracic pressure. The sharp reduction in blood pressure, due to reduction in venous return and cardiac output; the response as bar receptors into cause a reflex tachycardia and to a letter lesser extent peripheral vasoconstrictors. With the release of intrathoracic pressure, the venous return stroke volume and BP rise to higher than normal level, reflex parasympathetic influences than predominate and bradycardia results. Failure of the heart rate to risk during positive intra thoracic pressure indicates sympathetic dysfunction and failure of the heart rate to slow during Blood pressure overshoot indicates parasympathetic disturbance. In patients with autonomic failure, the fall in BP is not aborted during the last few seconds of increased intra thoracic pressure and there is no over shoot of BP when breath is released [34].

Vasomotor reactions

Measurement of the skin temperature is a useful index of vasomotor function. The integrity of sympathetic reflex arc which includes baroreceptors of the aorta and carotid sinus, their afferent pathways, the vasomotor centers and the sympathetic and parasympathetic outflow, can be tested in a

general way by the cold presser test, grip test, mental arithmetic test and Valsalva maneuver.

Vasoconstriction induces an elevation in Blood pressure. Similarly the sustained isometric contraction of a group of muscles for say 5 minutes normally increases the heart rate and the systolic and diastolic pressure by at least 15mmHg [34]. The response to both tests is impaired, particularly with lesion of the efferent fibers of the sympathetic reflex arc [34].

Sudomotor function

Test for integrity of efferent sympathetic pathway. In sympathetic or galvanic skin- resistance test, a set of electrodes placed on the skin measures the resistance to passage of weak current in skin, the change in electric potential is the result of a ionic current within sweat glands. The response defends on sympathetic response to sweat glands (Gutrecht)[32]. A more quantitative and reproductive method is examination of postganglionic sudomotor function termed QSART, developed and studied extensively by Low[33]. It is essentially a test of distal sympathetic axonal integrity utilizing the local axon reflex.

Autonomic dysfunction in HIV

Abnormalities in Autonomic nervous system occurring in HIV was first highlighted upon by Craddock et al.[5] As mentioned previously the prevalence varies from 5-77% according to definition and patient selection[10].

The cause of Autonomic dysfunction is unknown although HIV is neurotropic and has been isolated from peripheral nervous issues[58] and also depletion of autonomic axons in small bowel mucosa has been documented in HIV infected patients[61,62]. Even though HIV is associated with various form of cardiac involvement, underlying myocardial disease is not-implicated[11].

In the pre-AIDS stage of infection autonomic function appears to be intact, yet alteration in baroreceptor / vagal function associated with depressed myocardial function may be an early warning signal reflecting cardiovascular processes potentially exacerbated by HIV spectrum[35].

Patients with cardiac autonomic dysfunction where is severe stage compared to patients without autonomic dysfunction[36].

Treatment for Autonomic Dysfunction

Consists of

Non-pharmacological measures like adequate intake of salt and fluids, in the range of 10 to 20g, of salt / day and 2-3 litres of fluid / day.

Sleeping with the head end elevated will minimize the effects of supine nocturnal hypertension. Patients are advised to sit with legs dangling over the edge of the bed for several minutes before attempting to stand. Other maneuvers like leg–crossing, contraction of leg muscles for 30 seconds. Such measures compress leg vein and increase systemic resistance. Compression stocking may be helpful. Anemia should be corrected.

If above measures are inadequate, drug treatment is necessary Midodrine is effective in dose of 5-10 mg orally tid, but some respond to best to decremental dosage- (treatment `15 mg in morning, 10mg at noon at 5 mg at in a term non) Midodrine should not be taken after 6 pm, because it can aggravate supine hypertension, Pyridostigmine appears to improve orthostatic hypotension (OH). Fludrocortisone at dose 0.1 mg/day and 0.3 mg bid orally will effectively reduce OH, but aggravate supine hypertension. Potassium supplements are

necessary with chronic administration of fludrocortisone. Postprandial OH can be reduced by frequent small meals. Prostaglandin inhibitors taken with meals or midodrine can be used. Somatostatin analogue octreotide in dose of 25 μg bid to 100-200 μg tid acts by inhibiting gastrointestinal peptides prevent the vasodilation and hypotension effects.

Zidovudine appears to have major beneficial effect in treatment of HIV associated autonomic dysfunction[49,50] but some studies did not find any improvement in autonomic function with Zidovudine-treatment[38].

QTc – Interval and prolongation

QT interval taken from the onset of QRS complex to end of the 'T' wave and corrected for heart rate give the corrected QT interval (QTc). A QTc interval of more than 440 millisecond is considered prolonged [37].

QT interval prolongation is an irregularity of the electrical activity of the heart that places patients at risk for ventricular arrhythmias[39]. Patients with QT- prolongation are at high risk of serious ventricular arrhythmias usually, TdP, although monomorphic ventricular tachycardia may also develop[41].

QTc in HIV Disease spectrum

Patients with HIV disease have a significantly higher prevalence of QTc prolongation than a general hospital based population due to an acquired form of LQTS arising from HIV infection[41].

QTc prolongation and Drugs

Many of the drugs currently used in HIV positive patients, antibacterial, antifungal, psychotropic drugs and antihistamines have been associated with QT- prolongation[42]. Among the most important of risk factors is the concomitant use of drugs that share the CYP3A. Metabolic pathway. Since most protease inhibitors are potent inhibitors by CYP3A clinicians should be wary of this dangerous effect of HAART therapy. Pentamidine[43], trimethoprim sulfamethoxazole[44], Ciprofloxacin[45], Clarithromycin[41] are some of the drugs used in HIV infection to treat opportunistic infections which are associated with QTc prolongation. The drug induced QT prolongation is usually caused by blockade of human ether a-go-go- related gene (HERG) potassium channels and it has been shown that the HIV protease inhibitors (lopinavir, melfinavir, rifonavir and saquinavir) cause dose dependent block of HERG

channels suggesting that protease inhibitors would predispose individuals to QT prolongation and TdP[46].

Efavirenz, a novel non-nucleoside reverse transcriptase inhibitors, was also reported to cause QT- prolongation and severe ventricular arrythmias[47].

QTc – prolongation without previous recognized causes

Alteration in cardiac innervations have been described in HIV infection as mentioned previously and this has been evaluated as the cause of Autonomic-dysfunction[12,26].

Villa et al. studied the role of Autonomic – neuropathy in causing QTc prolongation in HIV infected persons [9].

Patients with dilated cardiomyopathy have been shown to have increased QT duration, QT- dispersion and increased variability of QT dispersion, reflecting variations in T-wave morphology, the factors which might predispose them to the development of arrhythmic events [48]. Kocheril et al.[40] – found a significantly higher prevalence of QTc – prolongation in HIV infected patients than general- hospital based population and proposed that it may be due to an unrecognized acquired form of long QT syndrome.

Treatment

This should be directed at removing precipitating factors ie : correcting metabolic abnormalities and removing drugs that have induced prolonged QT interval. In the setting of drug induced torsades de pointes atrial or ventricular over drive pacing and the administration of I.V magnesium have been useful in terminating and preventing arrythmias. Potassium channel – activating drugs such as Pinacidil and cromakalin may be useful in acquired forms of long QT- syndrome[51].

Material and Methods

MATERIALS AND METHODS

STUDY POPULATION

A total of 216 patients were enrolled for the study from the population of HIV infected patients who attended the out patient clinics of the institute of Internal Medicine, the ART clinic and the VCTC center. The patient attending the ART clinic were enrolled before they were started on HAART therapy.

141 patients was excluded as per exclusion criteria. The remaining 75 patients were selected for the selected for the study who satisfied all the inclusion and exclusion criteria. Written consent was obtained from all patients participating in the study.

Age and sex matched controls were also studied for comparison and meaningful interpretation of data. The controls were recruited from outpatient's clinic or were medical staff at the hospital. For HIV positive cases that were recruited from the wards, appropriate seronegative controls were recruited from the wards. All patients and controls were not from a single ethnic background.

Study duration

This study was conducted for a period of ten months from August 2005 to May 2006.

Study Design

To evaluate the role of HIV infection as the cause of cardiac autonomic dysfunction and the prevalence QTc – interval prolongation in patients with autonomic dysfunction, a single centre matched care- control study design was chosen.

Laboratory Methods

Testing for HIV 1 and 2 had seen performed on each patient using ELISA technique. For those with positive results on the first ELISA test a second more specific ELISA was used for confirmation. Western blot technique was not used for confirmation. All controls had been tested as HIV antibody negative by ELISA.

HIV positive patients were diagnosed as having AIDS, when these was AIDS defining opportunities infection or malignancy and a CD 4 count of less than 200 irrespective of the clinical stage of HIV infection[52]. HIV positive patients were

also classified as having AIDS based on clinical features according to NACO guidelines.

All patients and control did not appear clinically dehydrated None of the subjects were underweight as assessed by BMI calculated using the formula. (Wt in kg / (ht in mt)^2). Any subject treated for tuberculosis or diabetes mellitus, alcoholism, multiple system atrophy and other disorder known to affects the autonomic nervous system and drugs known to produce QT prolongation were excluded. Blood sugar, urea, creatinine, full blood count were checked to exclude anaemia, dehydration and adrenal insufficiency. Also serum calcium, which was corrected for serum albumin and serum potassium, was checked to eliminate metabolic causes of QT prolongation. CD4 count was performed for all HIV positive patients using flow cytometry. A routine X-ray chest and ECHO was not done for all patients.

Of the 75 HIV positive patients, only two patients had acquired HIV infection through blood transfusion and the rest 73 patients had acquired through heterosexual intercourse. Thirty patients had asymptomatic HIV infection and forty patients had AIDS.

METHODS

Detailed clinical history were taken from each patients and a completes review of their case notes performed. A complete clinical examination of the nervous system and cardiovascular system was done for each patient.

Tests for autonomic functions

On the day of testing patients and controls were instructed not to ingest caffeine containing products. All recordings the done 5-8 hours post prandially. Blood pressure was recorded manually using sphygmomanometer (Life line-model max) and heart rate was measured in the ECG lab using semiautomatic, electrocardiograph machine (Model Alpha 99 and BPL cardiart 6108). The time interval between two successive R waves and the QT interval was measured using a standard ruler. All the recordings were done with styli control set at 10mm/ mV and paper speed at 25 mm/sec. Five cardiac cycles were recorded per lead and a long lead II taken to serve as rhythm strip.

The methods used in testing autonomic function were similar to those used for assessing diabetic autonomic neuropathy by Ewing and Clarke[53] and Bennett et al[54]. Al patients and controls were subjected to a battery of five tests as detailed below:

Heart rate response to valsalva maneuver

The subject was seated quietly and them asked to blow into a mouth piece attached to a manometer, holding it at a pressure of 40 mm Hg for 15 seconds while a continuous electrocardiogram was recorded and the pressure is released while the ECG is still recorded for 20 beats. The maneuver was repeated three times with one minute interval in between and results were expressed as

Valsalva ratio = longest R-R interval after the maneuver ÷ shortest R- R interval being the maneuver.

The mean of the three-valsalva ratios was taken as the final value.

Heart rate (R-R interval) variation during deep breathing.

The subject was asked to breathe deeply at six breaths / min (Five seconds “in” and five seconds “out”) for one minute. An ECG was recorded throughout the period of deep breathing and onset of each inspiration and expiration was worked on ECG paper. The maximum and minimum R-R intervals during each breathing cycle were measured with a ruler and converted to beats / min. The results of the rest were expressed as the mean of the difference between maximum and minimum heart rates for the six measured cycles in beats / min.

Immediate heart rate response to standing

The test was performed with the subject lying quietly on a couch while the heart rate was recorded continuously on an electrocardiograph. The patient was then asked to stand unaided and the point at starting to stand was marked on ECG paper. The shortest R-R interval at or around the 15^{th} beat and the longest R-R interval at around the 30^{th} beat after starting to stand were measured with a ruler. The characteristic rate response was experienced by 30:15 ratios.

Blood pressure response to standing

This test measured the subject’s blood pressure with a sphygmomanometer while he was lying quietly. Then he was

made to stand up and the blood pressure again after one minute. The postural fall in blood pressure was taken as the difference between the systolic pressure lying and the systolic pressure standing. The test was in repeated three times and the mean systolic blood pressure was calculated.

Blood pressure response to sustained hand grip

The blood pressure of the patient was taken three times before the maneuver. A modified sphygmomanometer was used to sustain handgrip. The patient was asked to grip the inflatable rubber and apply maximum voluntary pressure possible. A reading from the attached mercury manometer was taken during maximum voluntary contraction. There after, the patient was asked to maintain 30% of maximum voluntary contraction for as long as possible up to five minutes. Blood pressure was measured at one minute intervals during the handgrip. The result was expressed as the difference between the highest diastolic blood pressure during the handgrip exercise and the mean of the three diastolic blood pressure readings before the handgrip began.

INTERPRETATION OF THE TEST WAS BASED ON THE WORKS OF EWING AND CLARKE[53].

Score	Blood pressure test		Heart rate variability test		
	Response to standing	**Response to handgrip**	**Valsalva ratio**	**Deep breathing**	**Response to standing**
0	≤10	≥ 16	> 1.21	≥ 15	≥ 1.04
1	11 - 29	11 – 15	-	11 – 14	1.01 – 1.03
2	> 30	≤ 10	< 1.21	≤ 10	≤ 1.00

For grading of cardiovascular autonomic function, results are classified into normal, borderline and abnormal (scores 0,1,2 respectively). An overall score ≤ 3 was considered normal, score > 3and < 8 were considered borderlines and score ≥ 8 were judged was abnormal autonomic function[56].

QT interval was taken from the onset of QRS complex to the end of T wave. QT was then corrected for heart rate using the Bazette's formule[37].

QTc interval = QT / (R – R) ½. A QTc interval more than 440

Millisecond is considered prolonged.

Inclusion criteria

1. Age more than 15 less than 60.

2. HIV positive patients confirmed by ELISA

Exclusion criteria

1. Age less than 15 and more than 60
2. blood pressure more than 140/90mmHg
3. Diabetes mellitus
4. Any history suggestive of premorbid cardiac disease
5. Alcoholism
6. Pregnancy and puerperium
7. Use of any drugs known to affect cardiovascular system
8. Cigarette smoking in excess of five sticks per day.
9. Patients who are underweight(BMI <19)
10. HIV patients on HAART therapy, antituberculous drugs
11. Patients with CNS lesions.

STATISTICAL ANALYSIS

Statistical analysis was carried out for 111 patients (40 AIDS 35 HIV positive without AIDS, 36 HIV negative) after categorizing each variable – Age, sex, BMI, autonomic function tests, autonomic dysfunction score, QTc interval and CD4 count were analyzed. One way Analysis of variance (ANOVA) was performed for comparison of means of more than two groups. The significance of difference between two proportions was indicated by the chi-square (x^2) statistic. The significance of difference in mean between two groups was calculated by student t-test. Variables were considered to be significant if ($P<0.05$). Intervariate analysis was done by using Pearson's r-value correlation.

Observations and Results

OBSERVATION AND RESULTS

TABLE - 1

Group	n	Mean	SD	One way ANOVA F-test
AIDS-	35	39.26	6.473	F=0.12 P=0.88 Not significant
AIDS+	40	38.83	6.652	
Control	36	38.50	6.536	
Total	**111**	**38.86**	**6.506**	

AGE VARIATION AMONG THE STUDY GROUPS

SEX DISTRIBUTION IN STUDY GROUPS

TABLE - 2

		Group						Significance
		AIDS-		AIDS+		Control		
		n	%	n	%	n	%	
Sex	Male	23	65.7	27	67.5	24	66.7	$\chi 2$=0.03 P=0.98 Not significant
	Female	12	34.3	13	32.5	12	33.3	
Group Total		**35**	**100.0**	**40**	**100.0**	**36**	**100.0**	

TABLE - 3

BMI COMPARISON AMONG STUDY GROUPS

	N	**Mean**	**SD**	**One way ANOVA F- test**
AIDS-	35	21.0869	0.66899	F=46.1 P=0.001 Significant
AIDS+	40	20.7290	0.59714	
Control	36	22.4514	1.10421	
Total	**111**	**21.4005**	**1.09973**	

MEAN AND SD OF AUTONOMIC FUNCTION TESTS IN THE THREE GROUPS

TABLE - 4

BP HANDGRIP

	N	**Mean**	**SD**	**One way ANOVA F-test**
AIDS-	35	12.2280	5.32830	F=18.28 P=0.001 Significant
AIDS+	40	11.8280	4.56186	
Control	36	17.0936	1.56770	
Total	**111**	**13.66**	**5.32440**	

SD – Standard deviation

ANOVA – Analysis of variance

TABLE - 5

BP STANDING

	N	**Mean**	**SD**	**One way ANOVA F-test**
AIDS-	35	11.52	5.367	F=43.96 P=0.001 Significant
AIDS+	40	16.07	5.191	
Control	36	5.83	3.420	
Total	**111**	**11.31**	**6.34**	

TABLE -6

HR STANDING

	N	**Mean**	**SD**	**One way ANOVA F-test**
AIDS-	35	1.1309	0.10617	F=14.83 P=0.001 Significant
AIDS+	40	1.0800	0.09457	
Control	36	1.2027	0.09420	
Total	**111**	**1.1358**	**0.10992**	

SD – Standard deviation

ANOVA – Analysis of variance

TABLE – 7

HR VALSALVA

	N	**Mean**	**SD**	**One way ANOVA F-test**
AIDS-	35	1.2737	0.11914	F=22.29 P=0.001 Significant
AIDS+	40	1.1778	0.14223	
Control	36	1.3669	0.09609	
Total	**111**	**1.2694**	**0.14378**	

TABLE - 8

HR DEEP BREATHING

	N	**Mean**	**SD**	**One way ANOVA F-test**
AIDS-	35	12.2897	4.23885	F=15.57 P=0.001 Significant
AIDS+	40	11.1863	6.08651	
Control	36	16.7283	2.10688	
Total	**111**	**13.3316**	**5.08876**	

SD – Standard deviation

ANOVA – Analysis of variance

TABLE - 9

MEAN AUTONOMIC DYSFUNCTION SEVERITY SCORE

	N	**Mean**	**SD**	**One way ANOVA F-test**
AIDS-	35	3.26	2.160	F=58.75 P=0.001 Significant
AIDS+	40	5.25	2.447	
Control	36	.36	0.867	
Total	**111**	**3.04**	**2.819**	

FREQUENCY DISTRIBUTION OF NORMAL (0-3),

BORDERLINE (4-7), ABNORMAL (8-10)

		Group						**Significance**
		AIDS-		**AIDS+**		**Control**		
		n	**%**	**n**	**%**	**n**	**%**	
Score	0-3	23	65.7	12	30.0	36	100.0	$\chi 2$=42.35 P=0.001 Significant
	4-7	9	25.7	15	37.5			
	8-10	3	8.6	13	32.5			
Group Total		**35**	**100.0**	**40**	**100.0**	**36**	**100.0**	

TABLE -10

MEAN QTc IN THREE STUDY GROUPS

	N	**Mean**	**SD**	**One way ANOVA F-test**
AIDS-	35	42.1991	1.99971	F=10.26 P=0.001 Significant
AIDS+	40	43.5063	2.68179	
Control	36	41.3672	1.18973	
Total	**111**	**42.4004**	**2.24571**	

FREQUENCY DISTRIBUTION QTc PROLONGATION IN

THREE STUDY GROUPS

		Group						**Significance**
		AIDS-		**AIDS+**		**Control**		
		n	%	n	%	n	%	
QTC	<44	30	85.7%	22	55.0%	36	100.0%	$\chi 2$=24.64 P=0.001 Significant
	>44	5	14.3%	18	45.0%			
Group Total		**35**	**100.0%**	**40**	**100.0%**	**36**	**100.0%**	

TABLE -11

MEAN CD 4 COUNT

	N	**Mean**	**SD**	**Student t-test**
AIDS-	35	398.17	106.552	t=110.84 P=0.001
AIDS+	40	157.70	91.273	
Total	**75**	**269.92**	**155.543**	

TABLE - 12

CORRELATION BETWEEN AUTONOMIC NEUROPATHY (AN)

AND QTc PROLONGATION IN TOTAL HIV POSITIVE CASE

	HIV + GROUP				**Significance**
	AN +		**AN -**		
	n	**%**	**N**	**%**	
QTc >44	23	62.16	-	-	$x^2 = 32.11$
QTc <44	14	37.83	38	100	P = 0.001
Group Total	**37**	**100**	**38**	**100**	**Significant**

TABLE - 13

CORRELATION BETWEEN AUTONOMIC NEUROPATHY (AN)

AND QTc PROLONGATION IN AIDS GROUP.

	AIDS GROUP						**Significant**
	AN (s)		**AN (m)**		**AN -**		
	n	%	n	%	n	%	
QTc> 49	7	53.84	11	73.33	-	-	x^2 =15.27
QTc<44	6	46.15	4	26.66	12	100	P=0.001
Group Total	**13**	**100**	**15**	**100**	**12**	**100**	**Significant**

TABLE - 14

CORRELATION IN BETWEEN AUTONOMIC NEUROPATHY

AND QTc PROLONGATION IN HIV + (AIDS-) GROUP.

	HIV + GROUP (AIDS NEGATIVE)						**Significant**
	AN (s)		**AN (m)**		**AN -**		
	n	%	n	%	n	%	
QTc> 44	1	33.33	4	50	-	-	x^2 =13.10
QTc<44	2	66.66	4	50	24	100	P=0.001
Group total	**3**	**100**	**8**	**100**	**24**	**100**	**Significant**

TABLE – 15

CORRELATIONS BETWEEN THE QTc PRLONGATION AND AUTONOMIC DYSFUNCTION SCORE USING PEARSON CORRELATION

		Score	CD 4	QTC
Score	Pearson Correlation	1	.202(*)	.638(**)
	Sig. (2-tailed)	0.00	.033	.000
	N	111	111	111
CD 4	Pearson Correlation	0.202(*)	1	-.011
	Sig. (2-tailed)	0.033	.	.906
	N	111	111	111
QTC	Pearson Correlation	0.638(**)	-.011	1
	Sig. (2-tailed)	0.000	0.906	.
	N	111	111	111

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

-1 to +1

Correlation denoted by r

Pearson correlation coefficient

0-0.2 Poor Correlation

0.2-0.4 Fair

0.4-0.6 Moderate

0.6-0.8 Good

0.8-1.0 V. Good

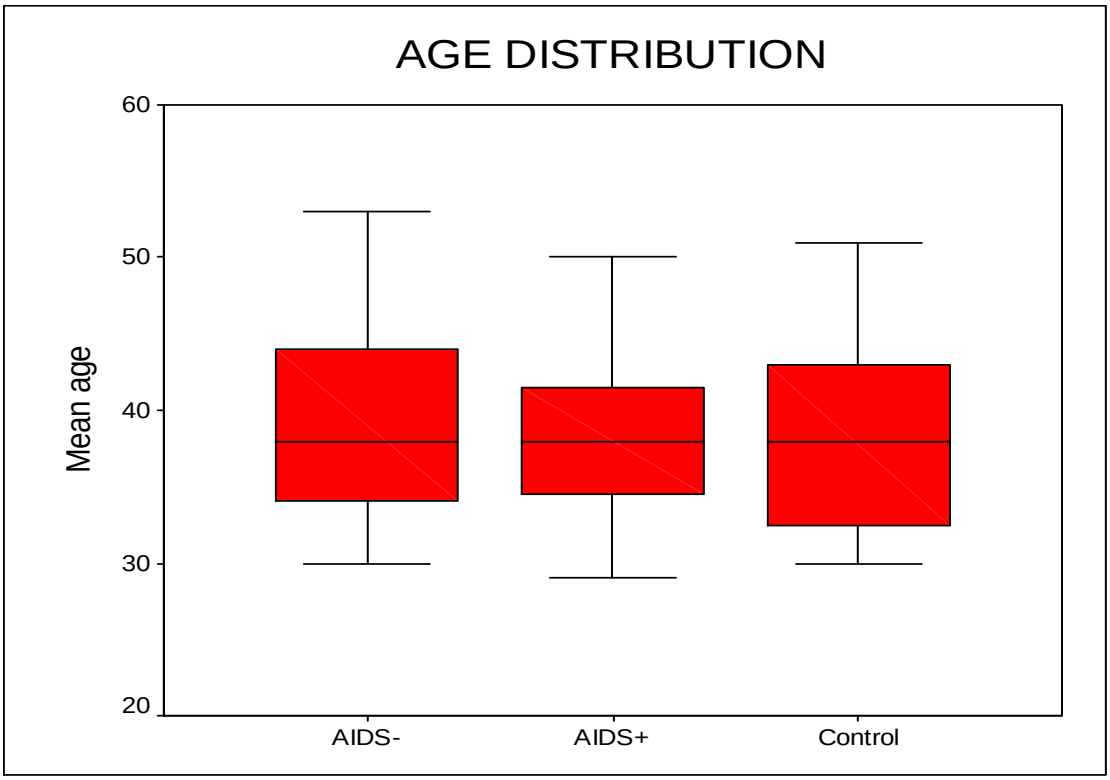

AGE DISTRIBUTION
Mean age
60
50
40
30
20
AIDS-
AIDS+
Control

Fig -1

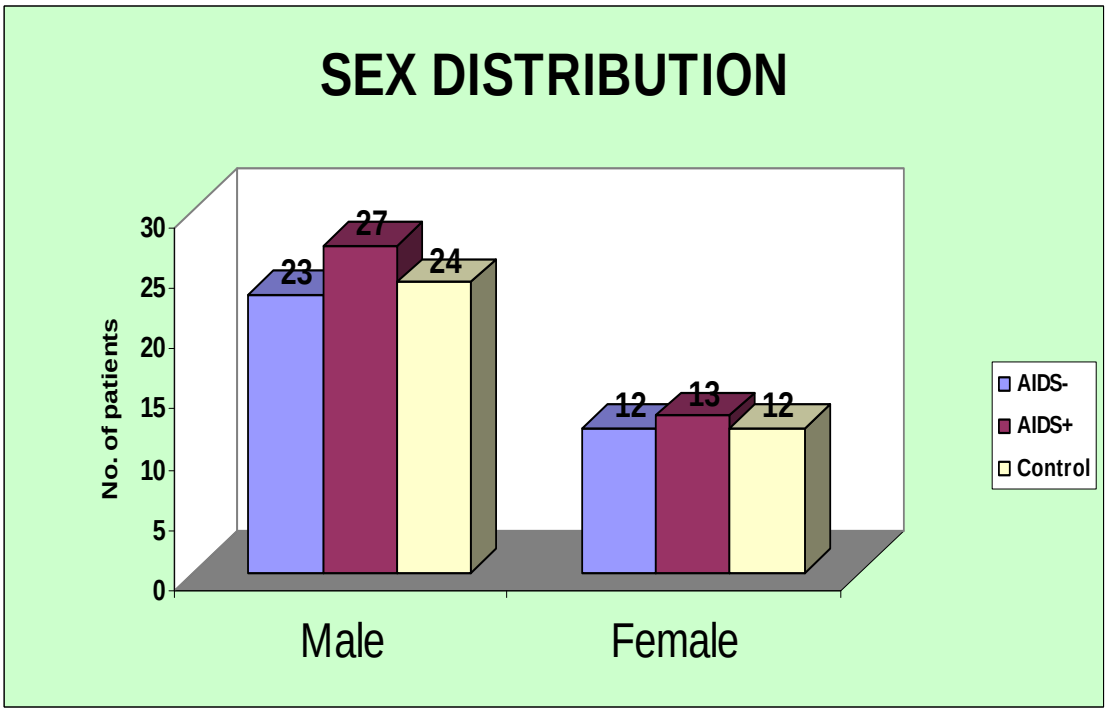

SEX DISTRIBUTION
No. of patients
30
25
20
15
10
5
0
23
27
24
12
13
12
Male
Female
AIDS-
AIDS+
Control

Fig -2

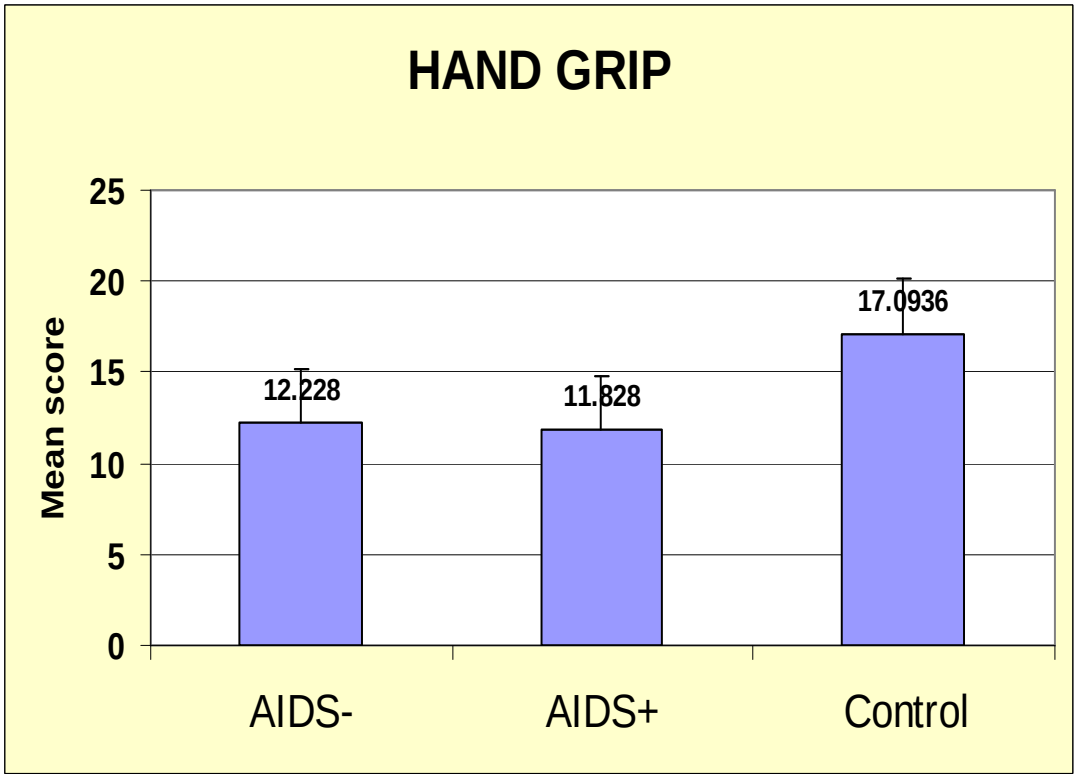

HAND GRIP
Mean score
25
20
15
10
5
0
12.228
11.828
17.0936
AIDS-
AIDS+
Control

Fig-3

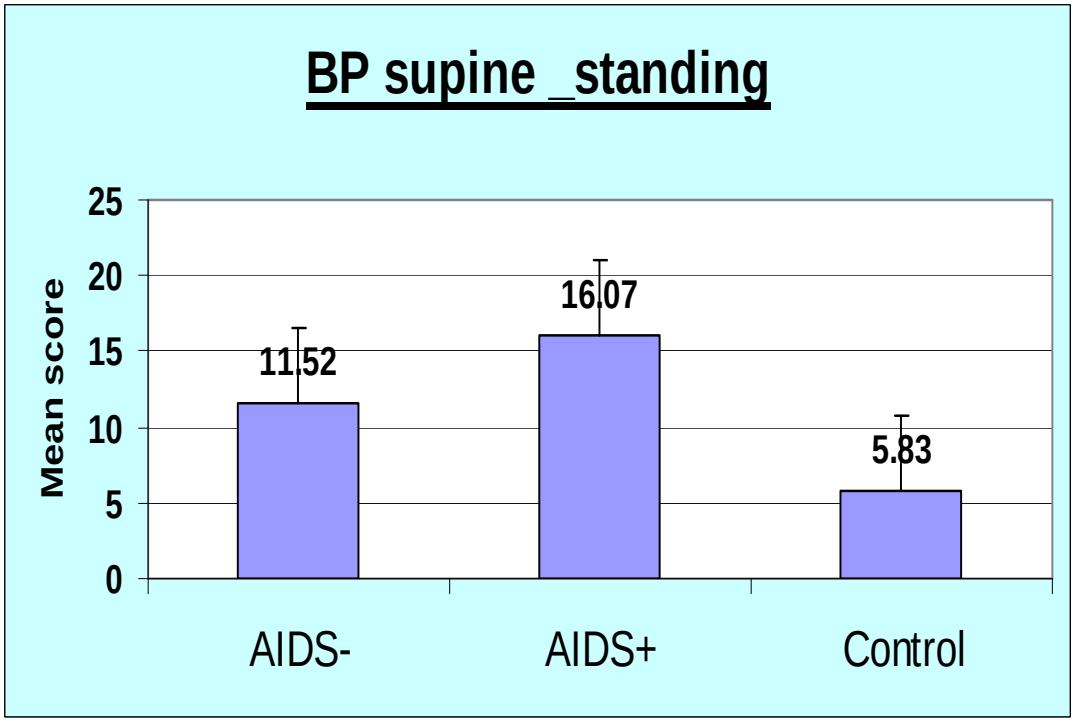
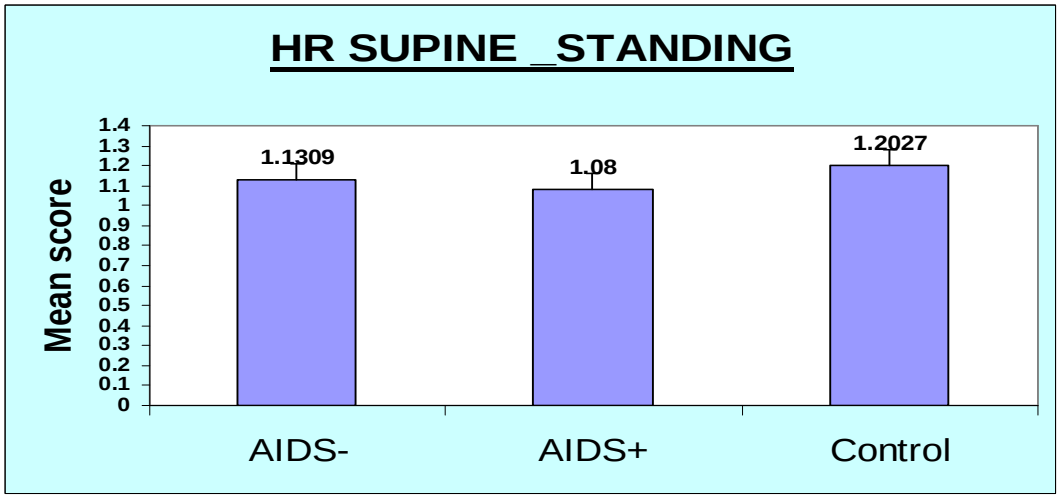
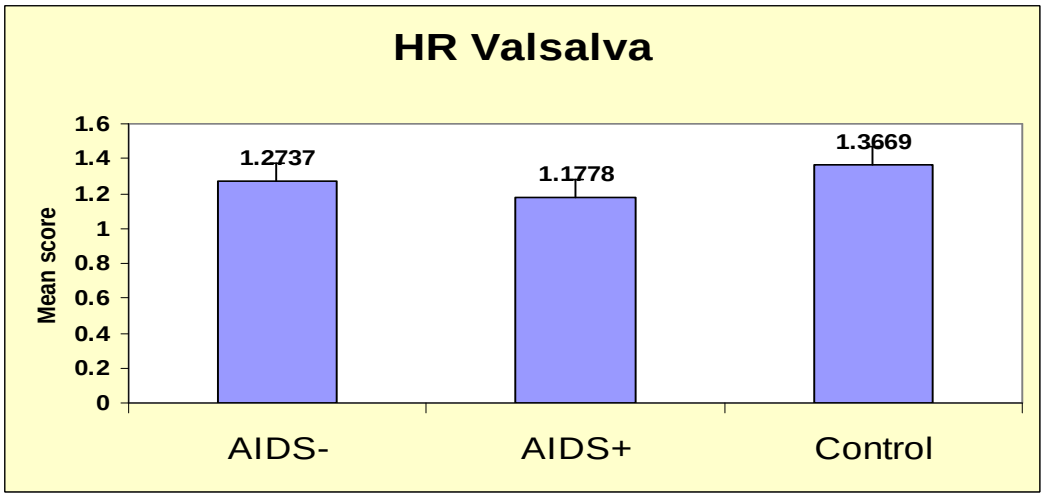

BP supine _standing
Mean score
25
20
15
10
5
0
11.52
16.07
5.83
AIDS-
AIDS+
Control

Fig-4


HR SUPINE _STANDING
Mean score
1.4
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.1309
1.08
1.2027
AIDS-
AIDS+
Control


HR Valsalva
Mean score
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1.2737
1.1778
1.3669
AIDS-
AIDS+
Control

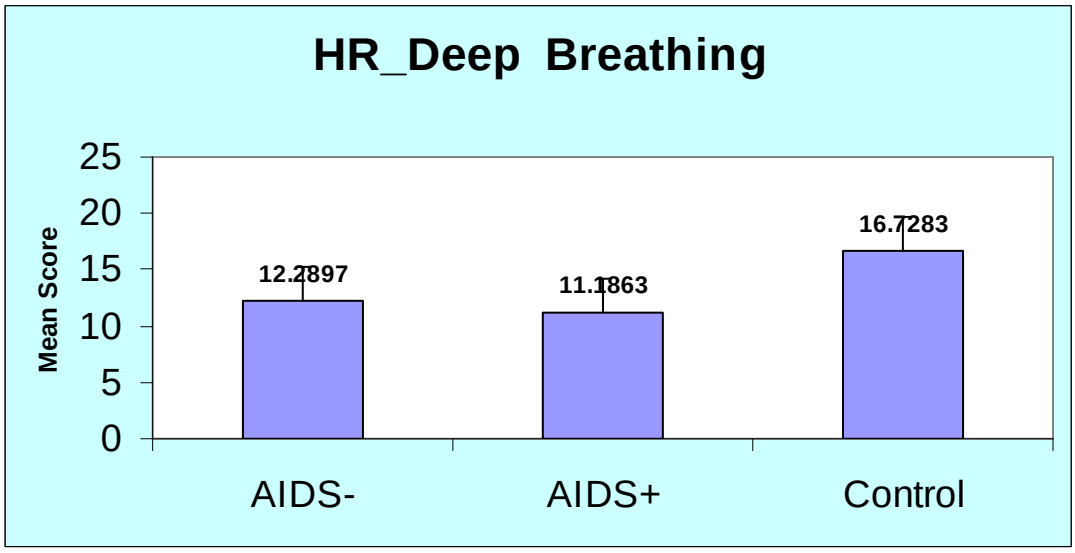
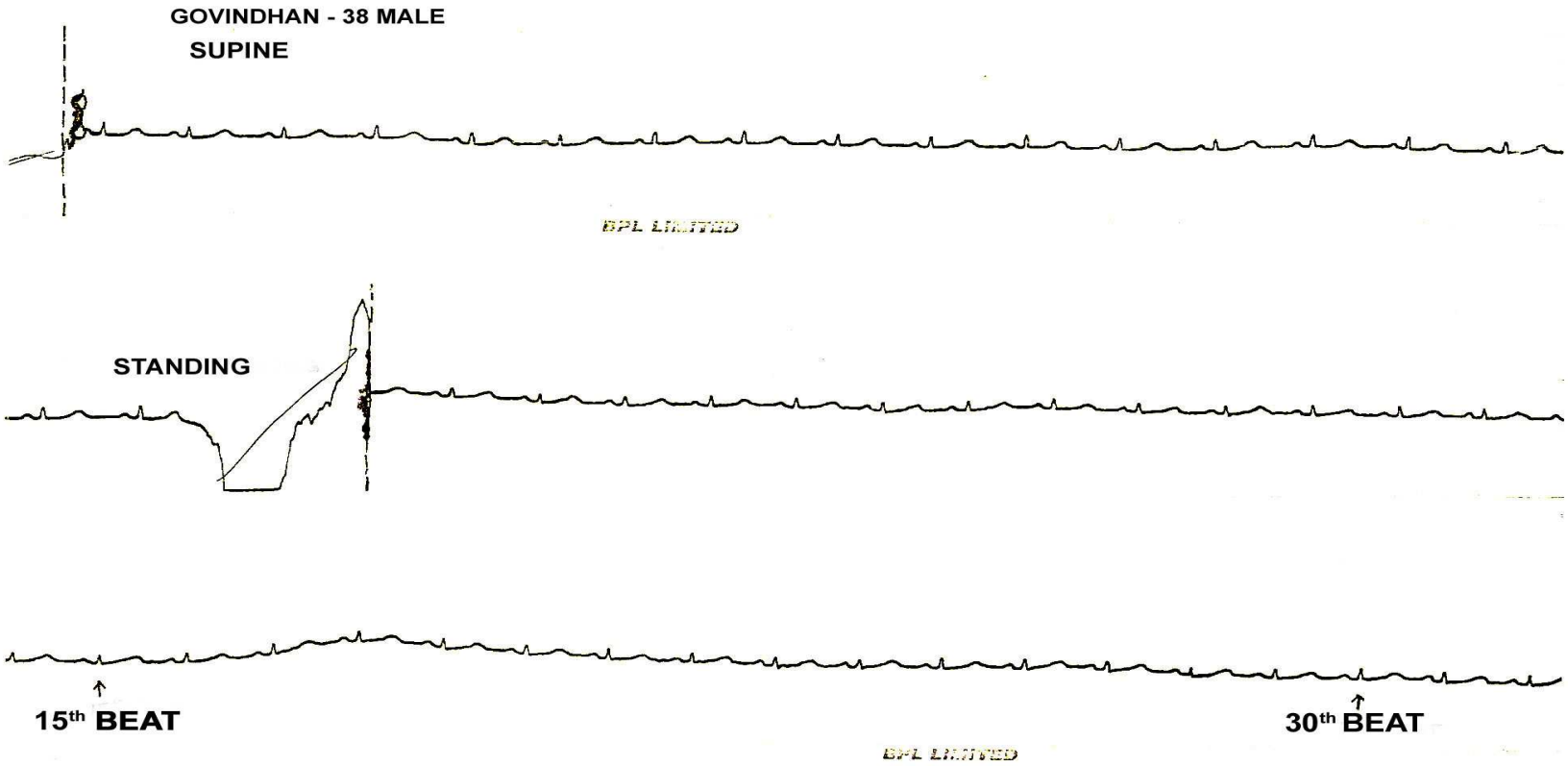

HR_Deep Breathing
Mean Score
25
20
15
10
5
0
12.2897
11.1863
16.7283
AIDS-
AIDS+
Control

Fig – 5, 6 & 7

SUPINE AND STANDING HEART RATE VARIABILITY

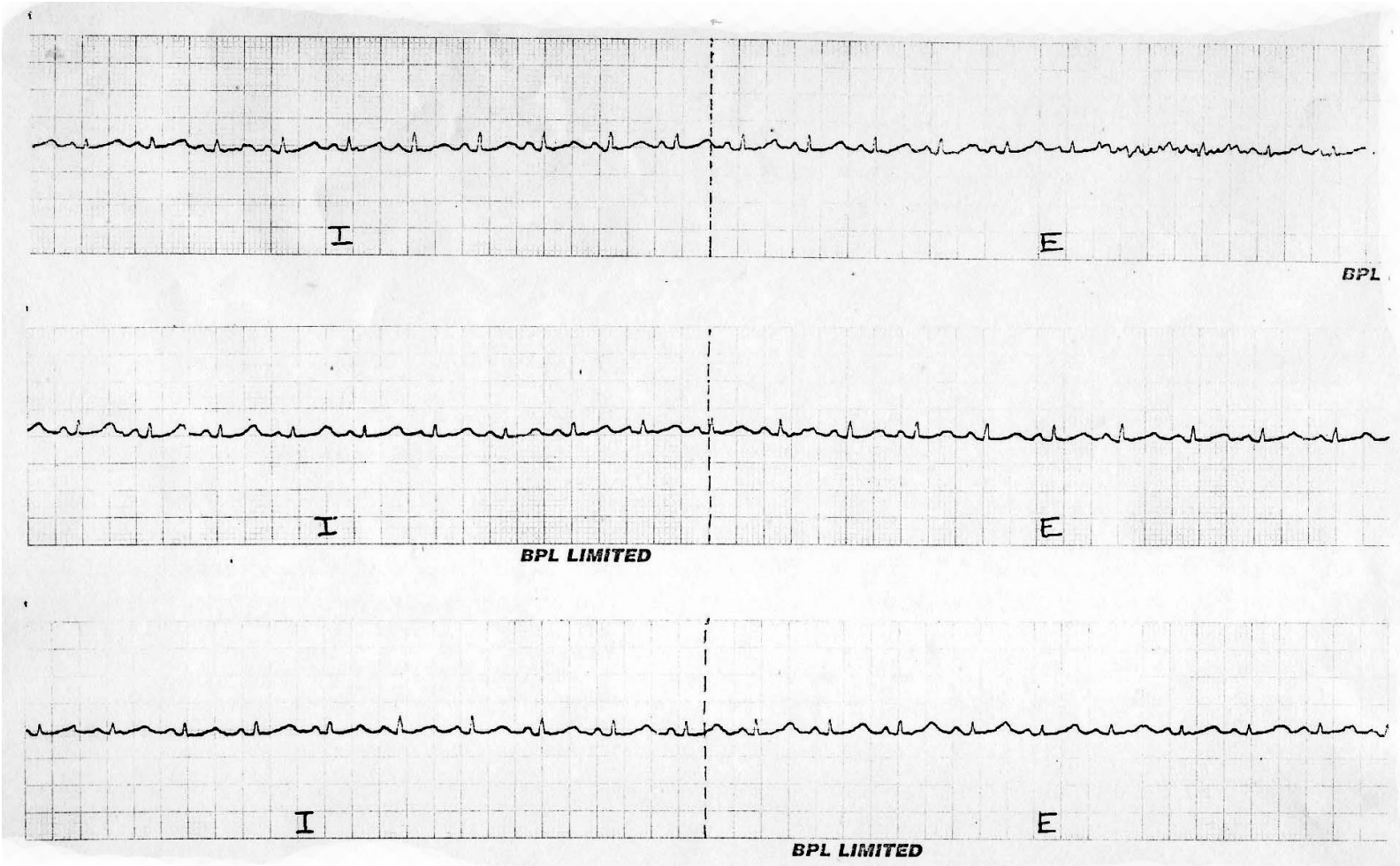


LII CONTINOUS RECORDING OF SUPINE AND STANDING - READ FROM LEFT TO RIGHT

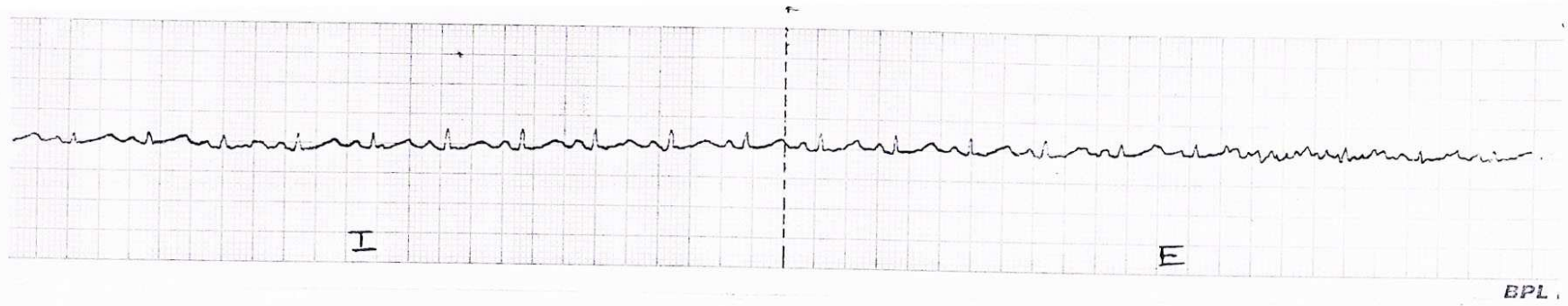
DEEP BREATHING HEART RATE VARIABILITY

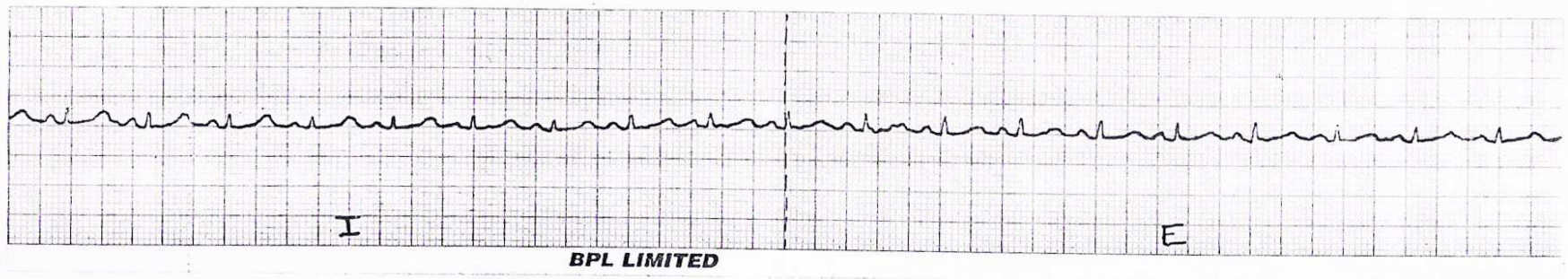
I- INSPIRATION PHASE
E- EXPIRATION PHASE

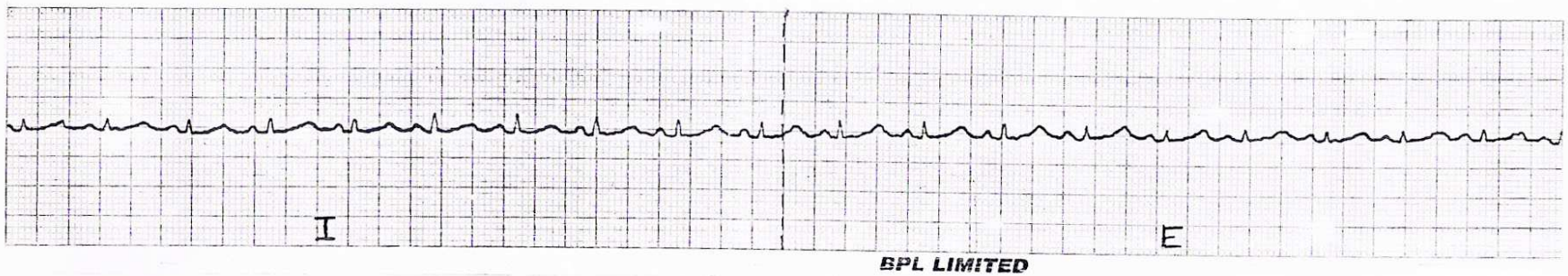
Cont.....2



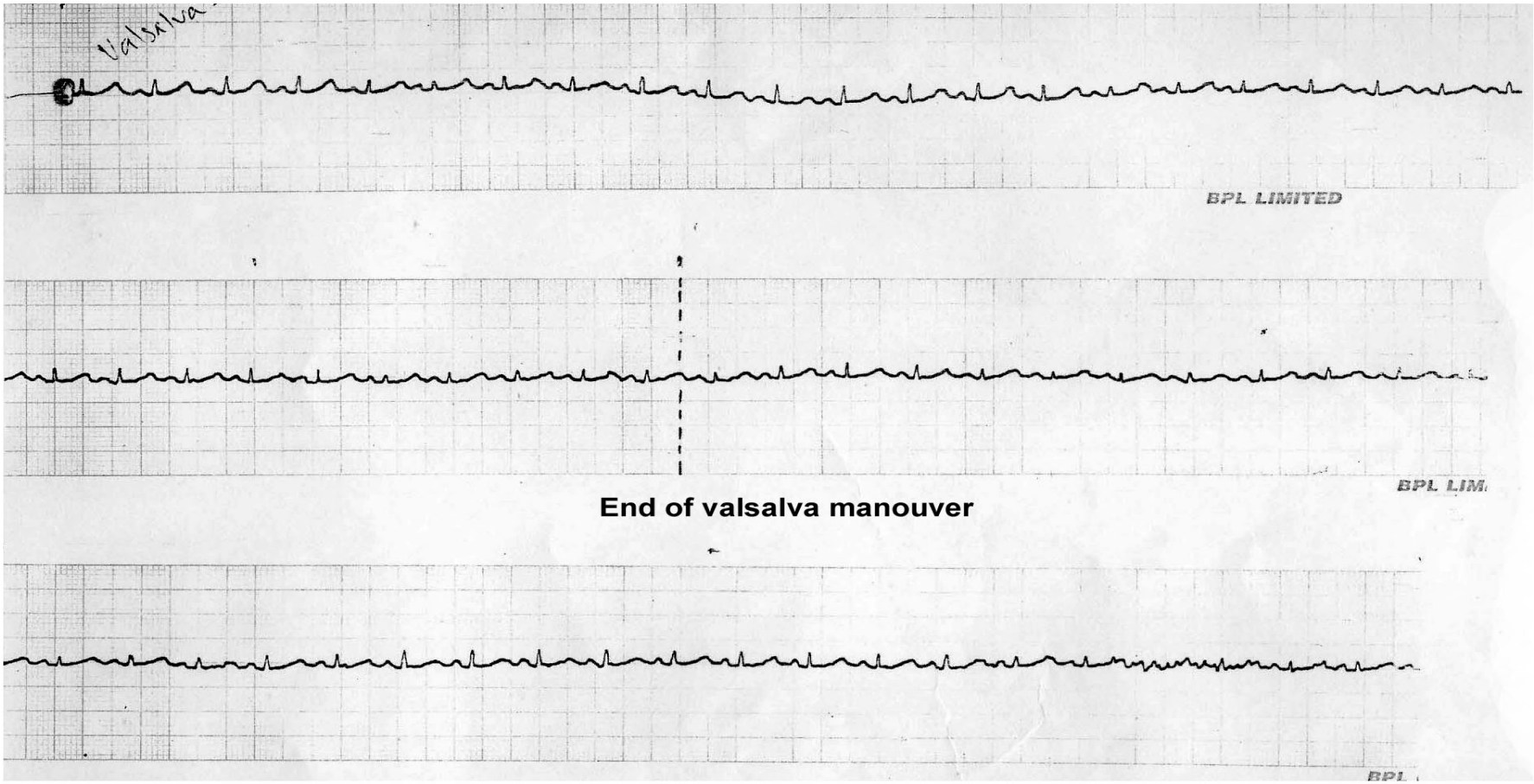
Cont.....3


I
E
BPL


I
E
BPL LIMITED


I
E
BPL LIMITED

VALSALVA MANOUVER HEART RATE VARIABILITY



A total of 111 cases were studied, 40, 35 and 36 for AIDS, HIV positive asymptomatic and HIB negative groups respectively. The mean age for the AIDS groups was 38.83, HIV positive (without AIDS) was 39.26 and HIV negative group was 38.56 (P=0.88). The percentage of females in the AIDS, HIV positive and HIV negative group were 32.5%, 34.3% and 33.3% (P=0.98). This shows that cases and controls were age and sex matched. The mean BMI in the three groups where AIDS (20.72), HIV+ (21.08) and HIV – (22.45). Of the 75 HIV the positive patients 40 patients were in stage 4 and 23 patients in stage 3, 12 patients in stage 2.

Only 20 patients had symptoms of peripheral neuropathy, of which 10 patients were with borderline autonomic dysfunction and 5 patients had severe autonomic dysfunction. Symptoms of autonomic dysfunction were present in only 18 cases out of 75 HIV positive patients. 14 patients belonged to the AIDS group and 4 patients belonged to the HIV positive (without AIDS) group. The symptoms of autonomic dysfunction correlated with severe autonomic dysfunction only in 8 patients and 5 patients had moderate autonomic dysfunction.

Tests for autonomic functions

The study showed statistical significance for all the tests of autonomic dysfunction between the cases and control groups, as all the tests had P values of less than 0.05.

The mean score (± 2 S.D) for the 3 groups where AIDS groups 5.25 ± 2.44, HIV positive group 3.26 ± 2.16 and the HIV group 0.36 ± 0.86 and (P=0.001) shows that the autonomic dysfunction is significantly different between the three groups. Thirteen patients in AIDS group have severe autonomic dysfunction (32%) compared to three in HIV positive group (80%). Also 15 patients in AIDS group (37.5%) had borderline dysfunction compared to 9 patients in HIV positive group (26%). This finding showed a significance of (P=0.01). If borderline dysfunction was also taken into account 37 patients (almost 54%) had evidence of autonomic dysfunction.

HR response to deep breathing was the most frequently abnormal (30 patients) followed by HR response to valsalva and BP response to hand grip (29 patients). The HR response to standing was the least abnormal (5 patients). In BP response to standing even though none of the patients had systolic blood

pressure of more than 30 mm Hg, patients shows significant difference between the groups (P=0.001).

QTc prolongation

Totally 23 out of 37 patients with autonomic neuropathy (AN) had QTc prolongation.

QTc prolongation was significantly different in the 3 groups (P=0.001) with 18 patients having prolonged QTc in AIDS group as compared to 5 patients to HIV positive (without AIDS) group.

The QTc prolongation was significantly different in cases with AIDS (AN) (combined severe and moderate autonomic dysfunction) compared to cases without autonomic dysfunction (AN-) (P=0.001 x^2 = 15.27. Similarly QTc was prolonged in HIV positive (AN+) when compared to QTc in HIV positive (AN-) group (P=0.001 x^2 = 13.10).

When comparing the autonomic function severity score and QTc, there was a highly significant positive correlation. Hence when the QTc interval prolongs the is also a increasing in the severity score.

Discussion

DISCUSSION

The results of this study on native Indian population illustrate the fact that cardiac autonomic dysfunction is common in HIV– infected patients of the sub – continent and that autonomic function deteriorates with progression to AIDS. Similar findings have been reported in previous studies[36,38,57]. This study demonstrated significant abnormities is autonomic function using basic cardiovascular autonomic reflex tests, which have well been validated [54,55].

Autonomic abnormalities were more readily apparent in tests for heart rate variation to deep breathing and valsalva ratio. In our study 30 patients had abnormal HR response to deep breathing followed by 29 patients who had abnormal blood pressure response to hand – grip land HR response to valsalva maneuver. Heart rate response to standing was least significant with only 5 patients having abnormal response.

The most pronounced abnormalities were found in patients with AIDS, but there was an trend of worsening autonomic function with progression of the disease as evidenced by the fact that the incidence of automatic

dysfunction was 34% in HIV positive cases and also the mean and were increases with the stage.

All the tests for autonomic dysfunction showed statistical significance (P=0.005). This is in contrast to the study by Rogstad et al.[56] which showed significant differences between AIDS patients and control for supine heart rate, valsalva ratio heart rate changes with cold phase test, but no significant difference in blood pressure and difference in heart rate to deep breathing, though there was a tread for worsening autonomic function with progression to AIDS. Divine Nizubontane et al[57] who studied HIV infected African patients showed significant difference in tests for blood pressure variability and valsava ratio but no significance heart rate response to deep breathing and standing. This divergence of results is probably related to difference in design, sample size, patient selection and grading of autonomic function test. Similar to both the studies this study showed increasing autonomic tester of were abnormal, suggesting that autonomic neuropathy could be an early indicator of HIV related neurological involvement.

A prolonged QTc was present in 5 out of 35 (14.3%) HIV positive patients and 18 out of 40 in the AIDS group (45%). This

shows that the prevalence of QTc prolongation increases when the patients move in the disease spectrum from HIV infection to AIDS, showing a probable role of disease process in the causation of prolonged QTc interval. After adjusting for the electrolytes, and known cause of QTc prolongation, QTc still differed significantly among the three groups (P = 0.001). QTc prolongation was significantly different in cases with AIDS (AN+) compared to AIDS (AN-) QTc prolongation was also significantly different in cases with HIV positive (AN+) when compared to HIV negative (AN-). Like wise a significant correlation was observed between autonomic function scores and QTc interval prolongation.

Villa et al[9] studied 57 HIV positive and 23 HIV negative subjects for the effect of alteration in cardiac innervations on QT- interval prolongation. 37 patients had autonomic neuropathy and QTc was prolonged in 24 out of 37 patients (64.8 %) with autonomic neuropathy and in 5 out of 20 HIV positive (with out autonomic neuropathy) patients, which has a sensitivity of 65 % and specificity of 75 %. This result is comparable to results obtained in our study.

In our study the abnormalities of autonomic function did not correlate with the patients having symptoms and clinical

features of peripheral neuropathy except in 5 cases with AIDS. Similarly only 8 patients had symptoms of autonomic dysfunctions. Nerve conduction studies were not performed to confirm these findings.

Previous clinical studies have shown both positive and negative results. Freeman et al[36] demonstrated significant abnormalities in autonomic function between 22 controls and 26 HIV positive patients.

Scott et al[59] carried out sequential autonomic tests on 22 patients, but found evidence of autonomic abnormalities in only one subject who also had AIDS related dementia. Villa et al studied 10 male and 5 female drug addicts, 10 of whom were HIV positive. They measured the R- R interval vaccination to deep breathing and found that two autonomic neuropathy and QTc was prolonged in 24 out of 37(64.8%) patients with autonomic neuropathy and in 5 out of 20 HIV positive / AN – patients (sensitivity 65%, specificity 75%), which is comparable to the results obtained in my study.

Kocheril et al[40] evaluated the etiology of LQTS in HIV infection. They observed a 7.0% prevalence of QT prolongation among non – HIV injected patients who served as controls. This

was however much lower than 29% prevalence among hospitalized patients with HIV during the same period (P=0.002) is the absence of a known cause.

Even though is our study the QTc prolongation was significantly different in cases with autonomic neuropathy compared to cases without autonomic neuropathy, a higher incidence was found in patients with moderate autonomic dysfunction (61%) compared to patients with severe autonomic dysfunction (39%) in the AIDS groups. Probably some other factors also played a role in QT prolongation in these patients, which has to be evaluated only in further studies.

A routine ECHO or a cardiac muscle biopsy was not done in the study and hence a myocardial disease a cardiomyopathy could not be ruled out. Patients with dilated cardiomyopathy have been shown to have increased. QT interval duration (Alonso et al)[48], but in our study we have excluded patients with history suggestive of cardiac dysfunction.

There were certain limitations in this study: Nerves techniques for measuring autonomic functions like the computer aided power spectral analysis of heart – rate variability (HRV) could not be done because of limitations is

resources and cost. A routine nerve conduction study was not done to assess the incidence of peripheral neuropathy in these patients. There was no facility for measuring serum magnesium. No Holter monitoring facility was available to assess the risk of ventricular tachycardia in patients with QTc prolongation. It was also not possible to do chromosomal studies to rule out the rate possibility of congenital LQTS.

The findings of autonomic dysfunction and QTc interval prolongation in HIV – infected subjects and AIDS patients portends danger. It means that apart from the other risk factors for cardiovascular disease, the danger of sudden death is real. In view of the risk of total cardio respiratory arrest, simple test such as the measurement of R- R interval variation could be useful in patients undergoing diagnostic invasive procedures, although it is unclear whether it would predict arrest. Zidovudine has been suggested in patients with HIV related neurological disorder[63], which may be also appropriate for treatment of patients with autonomic dysfunction. This study also confirms that QTc is a reliable parameter indicative the presence of autonomic neuropathy and since many days used in treating HIV infection are also associated with peripheral neuropathy and QTc prolongation it is suggested that back

ground QTc interval in individual patients be used to determine the type of drugs to be prescribed.

Conclusion

CONCLUSION

The following are conclusions from the study.

1. Cardiac Autonomic dysfunction is common in HIV infected patients, the probability of which is significantly increased with progression to AIDS.
2. The HIV positive asymptomatic subject have higher prevalence of QTc Prolongation compared to HIV negative subjective and as they moved to AIDS, the prevalence of QTc, prolongation increases.
3. A significant correlation is present between autonomic dysfunction and QTc prolongation. This makes QTc measurement as a reliable parameter of indicating the presence of cardiac autonomic dysfunction, but further studies are necessary to firmly establish the relationship between automatic dysfunction and QTc / prolongation.

Scope for Future Study

SCOPE FOR FUTURE STUDIES

This study conducted in our hospital based population has significant observation and potential therapeutic implications. A few questions remain unanswered. The most basic one in why only a part of the HIV infected patients are prone to get autonomic dysfunction and QTc prolongation. The exact cause of autonomic dysfunction is patients with HIV disease spectrum has to be elucidated by further studies.

There is no longitudinal prospective study demonstrating the exact prognosis in patients with autonomic dysfunction. The natural history of cardiac autonomic dysfunction regarding the percentage of people developing complications (e.g., postural hypotension, sudden cardiac arrest etc) has to be demonstrated by further studies.

The appropriate time to initiate HAART therapy in patients with autonomic neuropathy has to be further analyzed. Further work also needs to be done on the regimen for the prevention and treatment of their complication.

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Annexure

PROFORMA

- Name : • Age • Sex
- Residence
- I.P. No.
- Marital Status:
- Occupation
- Smoking / Alcohol Status
- History of Exposure

Blood Transfusion, Surgeries, etc

- Hist. Sugg. of Peripheral neuropathy : (Numbers, parenthesize, pain etc)
- Hist. Sugg. of Autonomic Neuropathy : (Postural giddiness, urinary disturbance, erectile dysfunction)
- History Sugg. of Immuno

Compromised state : Fever. 1 month / Weight loss

Chronic diarrhea / Recurrent URI / skin & Oral problem

- Examination: Height: Weight: BMI:

Vital Signs: Pulse: BP: RR:

- Examination of Nervous system:
- Examination of cardio vascular system:
- Clinical Stage of HIV:
- CD 4 Count:

TESTS FOR CARDIO VASCULAR AUTONOMIC FUNCTION				
	Test 1	Test 2	Test 3	Mean
I Valsalva Ratio				
ii Deep Breathing Test				
iii Heart rate response to standing				
iv BP Response to standing				
v BP Response to sustained Hand grip				

QT – Interval	Test	QTc	Mean
At Rest			
Max Tachycardia			
Max Bradycardia			

- ECG: Axis: PR: ARS duration
- Blood Sugar: Sr. Na^{+}: Sr. Ca^{2+}:
- Sr. Albumin: Sr. K^{+}

MASTER CHART

Sl.No	Name	Age	Sex	BMI	PN	AN	HIV stage	AIDS	BP handgrip	BP Standing	HR standing	HR valsalva	HR deep breathing	Score	QTc	CD 4
1	Govindhan	38	M	20.86	-	+	4	+	9.83	20	1.02	1.15	7.5	8	45.05	160
2	Kamala	34	F	19.56	-	-	4	-	8	12.5	1.03	1.43	7.88	6	44.5	358
3	loganathan	49	M	21.32	+	+	4	+	10.12	22.22	1	0.92	10	9	46.5	64
4	ganesan	35	M	20.55	-	-	3	-	14	14	1.32	1.31	20	2	43.68	430
5	periyasamy	36	M	21.2	-	-	3	-	12	21.5	1.3	1.07	14.38	5	41.87	454
6	kamalavathy	30	F	20.1	+	-	4	+	10	18.88	1.04	1.36	5.06	5	42.34	130
7	Saravanan	40	M	21.25	+	-	4	+	9.33	24.66	1.02	1.15	7.06	8	40.1	186
8	Murugan	32	M	20.48	-	-	4	+	17	20.83	1.04	1.31	18.16	1	39.64	168
9	Jegan	42	M	21.42	-	-	3	-	16.61	8.66	1.03	1.4	14.33	3	42	510
10	Manohar	36	M	21.65	+	-	4	+	9.5	24	1.15	1.32	13.66	4	44	174
11	Geetha	30	F	19.78	-	-	2	-	19.54	3.43	1.26	1.4	18.22	0	40.6	780
12	Selvarani	29	F	20.06	-	-	4	+	5.8	22.22	1.01	1.12	18.83	5	45.5	120
13	Arrokiyam	34	M	21.23	-	-	4	+	14.83	14.38	1.1	1.1	14	3	41.6	114
14	Marimuthu	31	M	21.45	-	-	4	+	9	22.6	1.01	1.16	6.23	8	46.06	108
15	Baskar	39	M	20.1	-	-	2	-	17.61	11.5	1.23	1.31	14.55	2	41	458
16	Sathish	37	M	19.85	-	-	4	+	15.38	13.42	1.2	1.27	14	3	40.1	524
17	Kamalbasha	37	M	21.6	-	-	3	-	4.16	12.56	0.92	1.12	12.66	8	42.55	320
18	Ravi	44	M	20.5	-	+	3	-	11.82	6.16	1.14	0.95	11.58	4	41.3	360
19	Gurunath	39	M	20.8	+	-	4	+	14.16	14.38	1.23	1.41	13.5	3	40.68	174
20	Pandian	47	M	21.34	-	+	3	-	7.5	19.16	1.03	1.35	10.5	3	39.75	274
21	Gopi	36	M	21	-	-	4	+	10.5	7.33	1.02	1.08	13.33	5	47.3	160
22	Kalaivani	30	F	20.3	+	-	3	-	5.88	3.2	1.06	1.36	10.66	1	40.08	310
23	sindhu	35	F	21.6	+	-	4	+	8.16	12.66	1.06	0.95	9.33	5	45.65	140
24	Milton	32	M	20.8	-		3	-	19	8.88	1.12	1.26	3.61	2	42.36	300
25	Mala	34	F	19.8	-	+	4	+	8.28	18.95	1.02	1.15	7.88	8	43.2	154
26	Munusamy	39	M	21.46	+	-	4	+	7.51	14.55	1.12	1.07	9.22	6	44.8	190
27	Palani	42	M	20.3	-	-	4	+	16.16	12.33	1.06	1.35	14	2	40.24	186
28	Prema bai	39	F	19.78	-	+	4	+	8.28	15.38	1.14	1.07	16.16	5	47.4	130
29	Krishnaveni	33	F	20.9	+	-	3	-	7.51	13.68	1.23	1.27	13.06	4	40.16	404
30	Vijaykumar	31	M	21.5	+	-	4	+	13.68	19.54	1.2	1	13.66	6	46.82	174
31	Karthik	35	M	20.35	+	+	4	+	12.33	20.68	1	0.92	9.33	8	48.8	96
32	Dhanam	36	F	21.8	-	-	4	+	18.23	4.53	1.16	1.41	7.5	1	40.1	130
33	Prabu	38	M	20.68	-	+	4	+	3.52	18.95	1.02	1.07	14.31	8	43.36	88
34	Pannerselvam	40	M	21.44	-	-	2	-	10.11	7	1.12	1.36	3.61	3	42.7	510
35	Backiyam	42	F	20.6	+	-	4	+	15.38	14.55	1.2	1.31	5.06	4	39.56	180
36	Vijayan	41	M	19.88	-	-	4	+	9.5	12.38	1.03	1.31	7.88	3	41.6	190
37	Chinnama	43	F	21.2	-	-	3	-	17.38	13.42	1.14	1.27	11.58	2	39.8	280
38	Padmanaban	45	M	21.5	+	-	3	-	5.8	19.58	1.01	1	14.33	8	42.88	340

MASTER CHART

Sl.No	Name	Age	Sex	BMI	PN	AN	HIV stage	AIDS	BP handgrip	BP Standing	HR standing	HR valsalva	HR deep breathing	Score	QTc	CD 4
39	Gomathi	38	F	20.76	-	-	4	+	13.68	12.33	1.06	1.07	9.58	7	45.1	118
40	Raju	48	M	21.1	-	+	4	+	4.87	21.42	0.85	0.92	7.5	9	45.64	74
41	Karunakaran	49	M	20.2	-	-	4	+	2.6	15.4	1.03	1	9.5	8	42.66	106
42	Mariammal	30	F	21.32	-	+	4	+	17.58	6.53	1.06	1.31	14.33	1	40.16	194
43	Babaraj	51	M	20.45	-	-	2	-	13.68	8.66	1.12	1.27	14	2	41.3	460
44	Chitra	35	F	21.25	-	+	3	-	8.28	12.33	1.21	1.36	6.11	5	42.46	350
45	Channa rao	55	M	21.18	-	-	4	+	12.33	14.55	1.21	1.15	7.88	6	45.5	120
46	Somasekar	54	M	20.5	+	-	4	+	5.2	12.38	1.01	1.07	9.33	8	43.46	110
47	Kondaiah	53	M	20.8	+	-	3	-	1.38	7.66	1.08	1.36	13.66	1	41	400
48	Joseph	48	M	21.68	-	+	3	-	13.52	13.33	1.12	1.23	14.55	3	43.6	324
49	Vijaya	41	F	21	-	-	4	+	16.66	16.66	1.02	1.31	11.58	4	42.33	140
50	Govindhammal	32	F	22.3	-	-	2	-	19.54	19.54	1.03	1.36	7.5	5	46.34	580
51	Gopi	30	M	20.3	-	-	4	+	20	20	1.12	1.3	12.55	3	40.7	170
52	Vijayalakshmi	40	F	19.8	-	+	4	+	22.22	22.22	1.03	1.12	5.06	8	46.42	160
53	Palaniammal	44	F	22.1	-	-	2	-	4.52	4.53	1.31	1.4	18.83	0	41.18	454
54	Ravi	36	M	21.25	-	-	3	-	20.06	20.06	1.03	1.07	5.58	8	47.08	330
55	Ramachandhar	37	M	20.46	+	+	4	+	15.4	15.4	1.32	1.3	6.23	5	45.6	130
56	Mustafah	49	M	21.15	-	+	2	+	9.5	7.51	1.31	1.36	14	2	39.53	520
57	Gajendhran	44	M	20.66	-	+	4	+	7.28	17	1.02	1.15	3.61	8	43.3	104
58	Devika	43	F	20.76	-	-	3	-	4.87	16.66	1.01	1.27	5.58	6	47.34	360
59	somaiya	50	M	21.43	+	-	4	+	12.33	14.16	1.16	1.15	13.58	5	46.06	108
60	Kesarnath	50	M	22.1	-	+	3	-	8.28	12.33	1.23	1.26	7.5	5	41.44	290
61	David	40	M	20.6	-	-	4	+	14.5	23.51	1	1.1	4.06	8	45.84	94
62	Chellapan	35	M	21.56	-	-	2	-	17.68	8.66	1.03	1.27	13.66	2	40.5	410
63	Sandhya	34	F	20.9	-	+	4	+	13.68	14.53	1.1	1.28	14.33	3	41.3	160
64	Devaki	33	F	21.06	-	-	2	-	18.16	6.42	1.12	1.3	15.06	1	39.85	520
65	Madhan	36	M	19.88	-	-	4	+	12.58	7	1.03	1.25	8.61	4	45.65	126
66	Kumari	35	F	20.12	+	+	4	+	16.23	12.66	1.02	1.31	40.06	3	40.6	134
67	Kandhasamy	40	M	21.8	-	-	3	-	17.56	6.53	1.06	1.27	14.33	1	42.55	410
68	Selvi	32	F	20.67	-	-	2	-	13.33	13.33	1.12	1.23	14.55	3	40.08	510
69	Pandian	47	M	20.43	-	-	3	-	14	12.38	1.32	1.31	20	2	41	340
70	Kesavan	36	M	22	+	-	3	-	12.16	21.5	1.3	1.07	14.38	5	44.68	480
71	Raman	33	M	21.9	-	+	3	-	16.61	8.66	1.03	1.4	14.33	3	39.96	320
72	muniyandi	38	M	20.78	-	-	2	-	13.83	14.38	1.1	1.27	14	3	42.36	440
73	Eswari	34	F	20.56	-	-	2	-	10.11	4.53	1.16	1.31	11.58	3	43.78	320
74	paulraj	39	M	20.8	+	-	3	-	5.88	3.2	1.06	1.36	10.66	1	43.1	290
75	Karuppaiah	48	M	21.6	-	-	3	-	17.61	13.42	1.2	1.35	13.33	2	42.14	260

HIV NEGATIVE CONTROLS

Sl.No	Name	Age	Sex	BMI	PN	AN	HIV	BP Handgrip	BP Standing	HR Standing	HR Valsalva	HR deep breathing	Score	QTc	
1	kandhan	32	1	22	-	-	-	17.38	0.6	1.12	1.3	12.66	0	40.1	0
2	kasthuri	33	2	20.16	-	-	-	16.16	1.12	1.06	1.36	14.55	0	41	0
3	sundharam	45	1	22.32	-	-	-	16.53	8.66	1.16	1.16	11.58	3	40.68	0
4	Munisamy	42	1	23.4	-	-	-	17	4.53	1.31	1.45	18.16	0	40.08	0
5	Hemalatha	36	2	23.2	-	-	-	16.73	5.53	1.21	1.31	18.83	0	42.36	0
6	Rajasekar	49	1	24	-	-	-	17.16	6.88	1.27	1.44	15.06	0	43.2	0
7	Rathnam	30	1	21.54	-	-	-	18.5	6.42	1.1	1.4	17	0	40.88	0
8	Lalitha	38	2	22.23	-	-	-	18.8	8.07	1.31	1.21	17.23	0	41.1	0
9	Hemnath	31	1	22.54	-	-	-	19.16	2.16	1.28	1.51	18.83	0	40.16	0
10	Aravindh	31	1	23.1	-	-	-	13.55	1.08	1.3	1.28	14	2	42.34	0
11	Kokila	32	2	22.8	-	-	-	17.61	3.23	1.21	1.31	16.73	0	42	0
12	Balamurugan	42	1	22.68	-	-	-	16.6	4.8	1.28	1.36	18.5	0	39.06	0
13	kannan	38	1	22	-	-	-	17.38	9.16	1.1	1.43	19.16	0	40.56	0
14	Rajashri	38	2	21.8	-	-	-	14.56	18.88	1.31	1.28	14.3	3	40.83	0
15	Vijayalakshmi	39	2	21.66	-	-	-	18.3	7.66	1.06	1.33	18.3	0	41.18	0
16	sivakumar	46	1	23.34	-	-	-	18.88	7	1.27	1.46	17.6	0	41.3	0
17	sukumar	51	1	22.41	-	-	-	16.73	8.06	1.12	1.27	17.33	0	42.66	0
18	Ramaraj	49	1	23.2	-	-	-	18.5	7.51	1.16	1.28	15.06	0	41.3	0
19	Manivel	38	1	22.18	-	-	-	17.68	6.66	1.12	1.4	18.16	0	40.5	0
20	Kavitha	34	2	22.43	-	-	-	16.73	4.53	1.087	1.23	16.16	0	40.06	0
21	Jayapal	51	1	23.8	-	-	-	17.16	2.42	1.21	1.35	17	0	39	0
22	Singaraj	32	1	22.18	-	-	-	16.88	1.2	1.27	1.31	17.23	0	39.8	0
23	Gagendren	45	1	21.4	-	-	-	13.68	1.8	1.12	1.45	13.66	2	42.53	0
24	Hemalatha	36	2	24.1	-	-	-	19.3	3.66	1.31	1.51	18.3	0	41.44	0
25	Lingaraj	39	1	23.8	-	-	-	17.16	6.53	1.33	1.43	19.55	0	42.3	0
26	Amaravathy	30	2	20.54	-	-	-	16.8	7	1.03	1.33	15.8	0	40.6	0
27	Iyyapan	44	1	22.6	-	-	-	19	7.5	1.36	1.57	17.38	0	43.68	0
28	Gomathy	33	2	21.9	-	-	-	18.88	8.66	1.21	1.28	16.73	0	42	0
29	Selvamani	50	1	24.14	-	-	-	17.38	9.51	1.1	1.36	18.83	0	41.6	0
30	Ramasamy	41	1	20.16	-	-	-	12.28	5.16	1.14	1.43	18.16	0	40.24	0
31	Radhika	40	2	22.34	-	-	-	16.73	6.73	1.08	1.51	17.58	2	42.88	0
32	Charles	31	1	24.32	-	-	-	16.79	6.66	1.31	1.28	14.33	0	43.1	0
33	Renumathy	35	2	22.12	-	-	-	16.66	4.16	1.23	1.38	19.16	0	42.36	0
34	Ranganathan	34	1	21.67	-	-	-	16.93	8.06	1.21	1.43	19.08	0	43.2	0
35	Elango	40	1	20.5	-	-	-	17.68	6.3	1.28	1.31	12.73	1	41.34	0
36	Murugan	31	1	23.69	-	-	-	18.12	2.16	1.27	1.51	17.5	0	41.8	0